REMARKS

Claims 1-7 are pending in this application. Claims 1-7 have been rejected under 35 U.S.C. § 112, ¶ 1 on the basis that they allegedly contain new matter not found in the application as originally filed. Claims 1-7 have also been rejected under 35 U.S.C.§ 103(a) as being obvious over (1) U. S. Patent No. 5,788,966 ("*Chess*"); (2) *Chess* when taken in combination with *Riikonen* and *Fabbri*; and (3) *Chess* in combination with *Riikonen*. The Examiner has also objected to the specification under 37 C.F.R. 1.821(d) on grounds that sequence identifiers were not provided for the primer sequences identified at page 30, lines 23-26.

Applicants respectfully maintain that the instant amendments to the specification and claim 1 overcome the Examiner's objection to the specification and new matter rejection, and that claims 1-7 are patentable over *Chess, Riikonen*, and *Fabbri* for the reasons provided hereinafter.

Please charge Biogen Deposit Account 02-2327 for all fees required in connection with the filing of the instant Response. If, for whatever reason, the Patent and Trademark Office will not charge those fees to Biogen Deposit Account 02-2327, authorization is hereby given to charge the fees in the alternative to Coleman, Sudol & Sapone Deposit Account 04-0838.

37 C.F.R. 1.821(d).

The specification has been amended to identify the primer sequences at page 30, lines 23-26 as SEQ ID NOs: 10-13. Applicants hereby submit a diskette containing a computer readable format (CRF) copy of these sequence listings, as well as a paper copy of the same. The contents of the paper and CRF copies are identical and include no new matter, as required by 37 C.F.R. 1.821(e). The sequences on the diskette and on the paper listing are identical to the sequences in the application as originally filed. Please charge any fees incurred in connection with this submission in accordance with the above-identified deposit account authorization.

35 U.S.C. § 112, ¶ 1.

Claims 1-7 as pending in the instant application have been rejected on grounds that the claim phrase "or equivalents thereof, or naturally occurring variants thereto" and

claim dosage ranges "of between about 10 mg to about 250 mg administered over a dosing period of between about one to about seven days", constitute new matter. In the interest of expediting prosecution, claim 1 has been amended to delete reference to "naturally occurring variants thereto". Otherwise, the application as originally filed disclosed methods that enabled those of ordinary skill to determine sequences equivalent to SEQ ID NO: 8, see, e.g., page 9, lines 2-9, and the recited dosage ranges fall within the ranges specified in the application as originally filed, e.g., at page 19, lines 3-8. Accordingly, the "equivalents thereof "and dosage limitations are not new matter and Applicants respectfully maintain that the Examiner should withdraw the rejection under Section 112, ¶ 1.

35 U.S.C. § 103(a).

Claims 1-7 have also been rejected under 35 U.S.C. § 103(a) as being obvious over (1) *Chess*; (2) *Chess* when taken in combination with *Riikonen* and *Fabbri*; and (3) *Chess* in combination with *Riikonen*. Per the Examiner:

> The '966 patent teaches a method for treating arthritis (see the entire document and column 10, reference claims 1-8 and column 8 line 65-67 in particular) that is associated with elevated levels of VLA-1 comprising administering to a human a monoclonal antibody 1B3.1 or a fragment thereto (column 3, lines 5-10) that inhibits collagen binding to VLA-1 (see entire document and reference claims 1-8, column 10 in particular). Furthermore, the '966 reference teaches that IB3.1 antibody recognizes an epitope on VLA-1 protein (see column 8, lines 39-46 in particular). The '966 patent further teaches that the increased prevalence of last state T cell activation antigen or VLA-1 in active juvenile chronic arthritis (column 1, lines 56-57 in particular).
>
> The claimed invention differs from the reference teachings only by the recitation of a function blocking antibody or fragment of said antibody, capable of binding an epitope of VLA-1, wherein the epitope consists of the amino acids of SEQ ID NO: 8, or equivalents thereof, or naturally occurring variants thereof and a dosage of between about 10 mg to about

250 mg administered over a dosing period of between about one to about seven days in claim 1. (Oct. 21, 2003 Office Action at page 3.)

The Examiner acknowledges that *Chess*: does not disclose the epitope defined by SEQ ID NO: 8; does not describe the dosages recited as limitations of the pending claims; and does not disclose the decreases in arthritic score that also constitute limitations of the pending claims. Despite all of these differences between *Chess* and the claimed invention, the Examiner finds the claims obvious because he believes that they merely reflect optimization of dosages and durations of known treatments. This misconstrues the claims and ignores the differences between *Chess* and the claimed invention.

Chess's disclosure that (1) the synovial fluid of arthritis patients expresses enhanced levels of VLA-11 (2) mAb 1B3.1 affects the interaction of VLA-1 and T cells in conditions where enhanced levels of VLA-1 are noted, and (3) that the synovial fluid of arthritis patients expresses enhanced levels of VLA-1, do not equate to the treatment regimen of the claims, in which a defined epitope is targeted, defined dosages are administered, and defined clinical endpoints are achieved. The key limitations of the pending claims are not minor variations of a specific treatment method disclosed in *Chess*. *Cf. Haynes International, Inc. v. Jessop Steel Co.*, 28 U.S.P.Q.2d 1652 (Fed. Cir. 1993), on reh'g, 29 U.S.P.Q.2d 1958 (Fed. Cir. 1994).

The manipulative differences between the steps of each of the pending claims and the disclosure of *Chess* constitute a detailed improvement over *Chess*. These differences establish that a significant aspect of the claimed invention is unexpected in light of *Chess* and refute the notion that the claims are unpatentable as obvious. *See Bristol Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 58 U.S.P.Q. 2d 1508 (Fed. Cir. 2001); *In re Eli Lilly & Co.*, 14 U.S.P.Q. 2d 1741 (Fed. Cir. 1990) (*prima facie* obviousness where claim not limited to details or improvements not shown in the art).

The Examiner has failed to establish a specific motivation in the art to modify *Chess* to result in the administration of an antibody or antibody fragment in a dosage of between about 10 mg to about 250 mg administered over a dosing period of between about one to about seven days to provide a decrease in arthritic score of about 65% or

greater when compared to a control antibody treated subject. The defined epitope, dosages and therapeutic endpoints recited in the claimed methods differentiate the claims from *Chess* and those key limitations cannot be ignored in assessing the patentability of the claims. *Rapoport v. Dement, et al.*, 59 U.S.P.Q. 2d 1215 (Fed. Cir. 2001).

The Examiner contends that *Chess*, *Riikonen*, and *Fabri* render the pending claims unpatentable as obvious.

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the I B3.1 monoclonal antibody taught by the '966 patent with functional monoclonal antibody FB12 as taught by Fabbri et al. in a method of treating rheumatoid arthritis.
>
> One of ordinary skill in the art at the time the invention was made would have been motivated to do so because FB12 monoclonal antibody has a functional role in lymphocyte binding to ECM protein as taught by Fabbri et al. a critical molecule in synovial lymphocytes of patients with rheumatoid arthritis as taught by Riikonen et al.
>
> From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. (Oct. 21, 2003 Office Action at page 5.)

The premise of this rejection is flawed because it assumes, without any support, that key claim limitations relating to epitope, dosage, and therapeutic endpoint were somehow known as the result of *Chess*, *Riikonen*, and *Fabri*. *Chess's* disclosure that monoclonal antibody 1B3.1 binds to a distinct VLA-1 epitope; *Riikonen's* disclosure that the mAb SR-84 blocks the function of $\alpha 1\beta 1$ integrin and that in HeLa cells $\alpha 1\beta 1$ integrin acts as a receptor for certain types of collagen; and *Fabbri's* disclosure that the FB12 mAb is functional in that it blocks the adhesion of activated T lymphocytes to

fibronectin, collagen type IV and laminin do not disclose the specific epitope target, dosages, and therapeutic endpoints recited in the pending claims.

The epitope target, dosage, and duration of treatment claim limitations are not "prior art elements [that] will perform their expected functions to achieve their expected results when combine[d] for their common known purpose." Office Action, page 6. *Fabbri* stated that FB12 mAb "may represent a useful reagent for the study of the biological function of α1-1 integrin I domain"; the reference did not specify that the FB12 mAb was a therapeutic agent that could target a specific epitope of VLA-1 to achieve a defined clinical result. *Fabbri* recognized that FB12 mAb might bind to ECM. However, by the time *Fabbri* reached this conclusion, *Riikonen* had published that ECM is found in the synovial lymphocytes of patients with rheumatoid arthritis. *Riikonen* did not lead *Fabbri* to conclude that FB12 mAb could be used to treat rheumatoid arthritis. Nor did *Chess* cite *Fabbri* or *Riikonen* in support of *Chess's* disclosure of therapeutic methods and compositions.

The references can only be modified and combined in the manner suggested by the Examiner through use of hindsight, and it is impermissible to employ such hindsight in rejecting the pending claims as being obvious in light of the prior art. Applicants respectfully submit that the Examiner has still not provided the requisite rigorous showing of a clear and particular suggestion, teaching, or motivation to combine *Chess*, *Fabbri*, and *Riikonen* to yield the claimed methods of treatment. *In Re Dembiczak,* 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).

The Examiner contends that *Chess* and *Riikonen* can be combined to render the pending claims obvious.

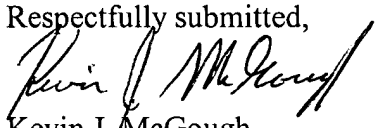
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the 1 B3.1 monoclonal antibody taught by the '966 patent with functional monoclonal antibody SR-84 as taught by Riikonen et al. in a method of treating rheumatoid arthritis.
>
> One of ordinary skill in the art at the time the invention was made would have been motivated to do so because SR-84 monoclonal antibody inhibits the adhesion of VLA-1 with different collagenous components of

extracellular matrix (ECM), and hence its important in $\alpha 1\beta 1$ integrin seen in synovial lymphocytes of patients with rheumatoid arthritis as taught by Riikonen at al. (Oct. 21, 2003 Office Action at page 6.)

In making this rejection, the Examiner ignores the key epitope, dosage, and clinical endpoint limitations of the claims, and asserts that he is free to do because those limitations are mere optimizations of known parameters. Neither *Chess* nor *Riikonen* disclose any of the key claim limitations. Even if *Chess* and *Riikonen* could be combined as suggested, they still would not yield those limitations and would not lead to the claimed methods of treatment. It is therefore incorrect to characterize Applicants' claimed invention as an optimization and combination of parameters found in one or more prior art references.

In light of all of the foregoing, it is respectfully maintained that the instant amendments and remarks address all of the grounds for rejection raised by the Examiner. Accordingly, Applicants respectfully maintain that all of the pending claims are allowable and should be passed to issue.

Respectfully submitted,



Kevin J. McGough
Reg. No. 31,279
Attorney for the Applicants
914-337-4082 (Office Number)

Of Counsel-Coleman, Sudol & Sapone
714 Colorado Avenue
Bridgeport, CT 06605-1601
(203) 366-3560
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